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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/981,547	10/17/2001	Jim Wells	SUNESIS.002DV1	8070

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EXAMINER	
EPPERSON, JON D	
ART UNIT	**PAPER NUMBER**
1639	

DATE MAILED: 12/29/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/981,547	WELLS ET AL.	
	Examiner	Art Unit	
	Jon D Epperson	1639	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *09 September 2003*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *58,59,61-66 and 81-87* is/are pending in the application.

4a) Of the above claim(s) *62-64 and 66* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *58,59,61,65 and 81-87* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. §§ 119 and 120

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

13)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application) since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

a) ☐ The translation of the foreign language provisional application has been received.

14)☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121 since a specific reference was included in the first sentence of the specification or in an Application Data Sheet. 37 CFR 1.78.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____.
4) ☐ Interview Summary (PTO-413) Paper No(s). _____.
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other:

DETAILED ACTION

Please Note: The Examiner respectfully requests Applicants to include with their next response a copy of all submitted and signed PTO-1449 forms because these forms were lost during the IFW scanning process.

Request for Continued Examination (RCE)

1. A request for continued examination (RCE) under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 10/9/03 has been entered. New claims 81-87 were added. Claim 58 was amended. Therefore, claims 58-59, 61-66 and 81-87 are pending. However, claims 62-64 and 66 remain withdrawn as being drawn to non-elected invention and/or species (see Paper No. 10). An action on the merit follows.

2. Those sections of Title 35, US code, not included in the instant action can be found in previous office actions.

Withdrawn Objections/Rejections

3. All outstanding rejections and/or objections are withdrawn in view of Applicants' amendments and/or arguments.

New Rejections

Objections to the Claims

4. Claim(s) 87 is objected to because of the following informalities:

A. Claim 87 is objected to because it depends on claim "96" which does not exist.

Claims Rejections - 35 U.S.C. 112, second paragraph

The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

5. Claims 58-59, 61, 65 and 81-87 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

A. **Claim 58**, recites the limitations "the compound", "said conjugate" or "said compound." There is insufficient antecedent basis for these limitations in the claims. Therefore, claim 58 and all dependent claims are rejected under 35 USC 112, second paragraph.

B. **Claims 59 and 61**, recite the limitation "the ligand." There is insufficient antecedent basis for these limitations in the claims. Therefore, claims 59, 61 and all dependent claims are rejected under 35 USC 112, second paragraph.

C. For **claim 82**, the term "associated" is vague and indefinite. For example, it is not clear how the –SH group is "associated" with the cysteine. Consequently, the metes and bounds of the claimed invention cannot be determined. Therefore, claim 82 is rejected under 35 U.S.C. 112, second paragraph.

D. **Claims 83-85**, recite the limitation "the library." There is insufficient antecedent basis for these limitations in the claims. Therefore, claims 83-85 and all dependent claims are rejected under 35 USC 112, second paragraph.

E. **Claim 87**, recites the limitations "the compound." There is insufficient antecedent basis for these limitations in the claims. Therefore, claim 87 is rejected under 35 USC 112, second paragraph.

Claim Rejections - 35 USC § 103

6. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

7. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

8. Claims 58-59, 61, 65 and 81-87 are rejected under 35 U.S.C. 103(a) as being unpatentable over Kim et al (WO 98/11436) (Date of Patent is **March, 1998**) (see IDS, entry No. 9) and Siuzdak (Siuzdak, G. Mass Spectrometry for Biotechnology. New York: Academic Press. **1996**, pages 119-126).

Kim et al (see entire document) disclose a method for screening a combinatorial library for ligands including non-oligomeric organic compounds that do not have a high affinity for a target macromolecule using "tethering" techniques (see Kim et al, page 1, paragraph 1; see also page 2, paragraphs 1-2). For example, Kim et al teach obtaining a target protein comprising a –SH group, masked –SH group, or activated –SH group (e.g., see Kim et al, claims 1-2, "target molecule, as obtained or as modified, contains one member of a binding pair ... wherein the binding partner and the reactive moiety are each a free sulfhydryl group [i.e., an –SH group] or a sulfur moiety which is available for disulfide bond formation through exchange"; see also page 3, paragraphs 2-3). Kim et al also teach combining said target protein with a library simultaneously containing at least two non-oligomeric ligand candidates wherein said ligand candidates each comprise a disulfide bond under disulfide exchange conditions, in the presence of a reducing agent (e.g., see Kim et al, see also page 11, paragraph 2, "As obtained, a target molecule might also include a binding partner (such as a sulfur moiety within a cysteine residue) which is available or can be made available (e.g., as a free sulfhydryl group or sulfur that is available for disulfide bond formation through exchange) for binding with a reactive moiety. If such a target molecule is used potential ligands [i.e., at least 2] can be

modified to include a free sulfhydryl group or a sulfur that is available for disulfide bond formation through exchange ... Here, non-specific binding of target molecule and potential ligands occurs through formation of a disulfide bond"; see also page 17, paragraph 1 disclosing the use of reducing agents, "non-specific interaction (here, disulfide bond formation) can be varied by adjusting the concentration of external ... reducing agents ... for example ... glutathione").

Kim et al does not explicitly state that the ligands are "less than about 2000 daltons in size" or "less than 1500 daltons " or "less than 750 daltons" (see claims 58, 59 and 61), but Kim et al does disclose ligands selected from the group consisting of "small organic molecules, pharmaceuticals, toxins" (see Kim et al, page 21, lines 15-20; see also claim 3 further disclosing "steroids, hormones, caffeine, ATP, cyclosporin, cyclophilin"), which would encompass molecules that are less than 750 daltons in size. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best,* 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Furthermore, Kim et al does not explicitly state that the target protein is a "TNF receptor" (see claim 65), but Kim et al does disclose ligands that are "membrane proteins", which would encompass proteins like TNF receptors because TNF receptors are "membrane proteins" (e.g., see claims 12, 43). "When the PTO shows a sound basis

for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Furthermore, Kim et al does not explicitly state that the library must comprise "at least 25 members" or "at least 100 members" (see claims 84-85), but Kim et al does state that libraries are produced using the split and pool synthesis techniques taught by Lam (e.g., see Lam, K. S.; Salmon, S. E.; Hersh, E. M.; Hruby, V. J.; Kazmierski, W. M.; Knapp, R. J., "A new type of synthetic peptide library for identifying ligand-binding activity" Nature **1991**, 354, 6348, 82-4), which teaches the formation of libraries with greater than 100 members. "When the PTO shows a sound basis for believing that the products of the applicant and the prior art are the same, the applicant has the burden of showing that they are not." *In re Spada*, 911 F.2d 705, 709, 15 USPQ2d 1655, 1658 (Fed. Cir. 1990). The Office does not have the facilities to make such a comparison and the burden is on the applicants to establish the difference. See *In re Best*, 562 F.2d 1252, 195 USPQ 430 (CCPA 1977) and *Ex parte Gray*, 10 USPQ 2d 1922 1923 (PTO Bd. Pat. App. & Int.).

Furthermore, Kim et al disclose the formation of a target protein-ligand conjugate (e.g., see Kim et al, claims 1-2; see also page 3, paragraphs 2-3; see also page 9, line 14; see also page 14, paragraph 1; see also page 28, paragraph 1, "This experiment illustrates

under conditions wherein a specific interaction between a target molecule and ligand can take place, preferential formation of disulfide-mediated ligand-target heterodimers [i.e., a target protein-ligand conjugate] can be observed"). Furthermore, Kim et al disclose that the target-ligand conjugate can be separated from the mixture (e.g., see Kim et al, page 3, lines 24-26, "Optionally, the complex of the ligand specifically bound to the target molecule can be separated or removed from the library or collection").

Finally, Kim et al also disclose determining the identity of the non-oligomeric ligand present in said target protein-ligand conjugate (e.g., see Kim et al, abstract, "Non-specific affinity enhancement as a method of identifying and detecting members, such as ligands ... in a collection or library of potential ligands"; see also Summary of the Invention; see also page 8, lines 18-20).

The prior art teachings of Kim et al differ from the claimed invention as follows:

Kim et al is deficient in that it does not specifically teach the use of mass spectrometry.

However, Siuzdak teaches the following limitations that are deficient in Kim et al:

Siuzdak (see entire document) teaches the use of electrospray mass spectrometry to study both "non-covalent" and "covalent" antibody-antigen interactions including fragmentation techniques like MS^2 and MS^3 (see pages 119-126, especially figures 6.3-6.6 and Table 6.1).

It would have been obvious to one skilled in the art at the time the invention was made to "identify" target/ligand interactions using the method steps as taught by Kim et al in conjunction with the mass spectrometer techniques as taught by Siuzdak because

Siuzdak explicitly shows that the technique can be applied to both "covalent" and "non-covalent" including antibody-antigen interactions (see Siuzdak, figures 6.3, 6.5; see especially paragraph bridging pages 125-126, "Electrospray mass spectrometry has also demonstrated its potential in the analysis of non-covalent interactions between an antibody and a hapten, and for observing covalent protein-bound intermediates in an antibody-catalyzed reaction"), which would encompass the "antibody-antigen" complexes disclosed by Kim et al (e.g., see Kim et al, page 4, lines 7-8 disclosing antibody-antigen reactions; see also lines 18-19 disclosing both "covalent" and "non-covalent" interactions). Furthermore, one of ordinary skill in the art would have been motivated to use the mass spectrometers as taught by Siuzdak with the antibody-antigen conjugates as taught by Kim et al (or any other target-ligand interaction) because Siuzdak explicitly states that electrospray has "demonstrated its potential" for these systems (see Siuzdak, page 126, paragraph 1).

Furthermore, one of skill in the art would be especially motivated to use mass spectrometry as disclosed by Siuzdak et al with the "antibody-antigen" complexes as described by Kim et al because Siuzdak et al discloses that BOTH "covalent" and "non-covalent" interactions can be measured (and distinguished) using a mass spectrometer (see Siuzdak et al, page 123, paragraph 3, "Declusterin potentials on the order of 70 V or greater usually promote the dissociation of noncovalent complexes as well as covalent fragmentation, while lower potentials (<70 V) are conducive to the observation of noncovalent complexes (protein complexes have been analyzed at declustering potentials of 40 V). In order for the method of Kim et al to work the modified antibodies must bind

"covalently" to their respective antigens (see Kim et al, figure 1 disclosing the covalent attachment of an antigen to a sulfhydryl group on the modified antibody). Therefore, any analytical technique that can confirm the "covalent" attachment of the antigen to the modified antibody is particularly useful. Consequently, a person of skill in the art would be motivated to "identify" even a "known" ligand using a mass spectrometer to determine the type of interaction (i.e., covalent v. non-covalent) to ascertain whether the modified ligand is truly able to bind to its respective target via a "covalent" bond as required by the method. Consequently, a person of skill in the art would be motivated to search for the "modified" ligands and/or targets as disclosed by Kim et al with electrospray mass spectroscopy as disclosed by Siuzdak et al to find modified ligands that can "covalently" bind to the targets as opposed to any unwanted "non-covalent" interactions that might occur.

Finally, one of ordinary skill in the art would have reasonably expected to be successful because Siuzdak shows many examples of target-ligand interactions that have successfully been analyzed on a mass spectrometer including antibody-antigen (e.g., see figures 6.3 and 6.5).

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jon D Epperson whose telephone number is (703) 308-2423. The examiner can normally be reached Monday-Friday from 8:30 to 4:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Andrew Wang can be reached on (703) 306-3217. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 872-9306 for regular communications and (703) 872-9307 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-2439.

Jon D. Epperson, Ph.D.
December 20, 2003

PADMASHRI PONNALURI
PRIMARY EXAMINER